PB88-180278

Health Effects Assessment for Heptachlor

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jun 87

U.S. Department of Commerce
National Technical Information Service
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TECHNICAL REPORT DATA
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1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/8-88/042		PB88 180278/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Heptachlor	June 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	47
	20. SECURITY CLASS (This page)	22. PRICE
	Unclassified	PC $12.95/MF $6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-180278

EPA/600/8-88/042
June, 1987

HEALTH EFFECTS ASSESSMENT FOR HEPTACHLOR

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
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SPRINGFIELD, VA. 22161

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with heptachlor. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Heptachlor. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-052. NTIS PB81-117632.

U.S. EPA. 1987. Drinking Water Criteria Document for Heptachlor, Heptachlor Epoxide and Chlordane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Report.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Heptachlor has been shown to be carcinogenic following oral administration in mice and rats. Based on the geometric mean of the incidence of hepatocellular carcinoma in mice in the two studies, a human q_1^* of 4.5 $(mg/kg/day)^{-1}$ has been derived (U.S. EPA, 1986c). The carcinogenic potential of heptachlor following inhalation exposure has not been studied so that an inhalation q_1^* cannot be derived.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
bw	Body weight
CBI	Confidential Business Information
CS	Composite score
DNA	Deoxyribonucleic acid
HA	Health advisory
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SMR	Standardized mortality ratio
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTY AND FATE

Selected physical and chemical properties and environmental fate of heptachlor are listed in Table 1-1.

The atmospheric half-life of vapor phase heptachlor is based on the estimated rate constants for its reactions with photochemically generated hydroxyl radicals and ozone (U.S. EPA, 1986a). Degradation by direct photolysis is not reflected in this half-life value, although it may also be a significant removal mechanism (NLM, 1986). The part of heptachlor that remains sorbed onto atmospheric aerosols will show a longer half-life. Monitoring data indicate that bioconcentration in aquatic organisms and adsorption to suspended solids and sediments are important fate processes of heptachlor in aqueous systems (Callahan et al., 1979; IARC, 1979). Hydrolysis is reported to be the dominant degradation pathway of heptachlor in the free state in water (Callahan et al., 1979). The half-life in the sorbed state will be considerally longer, however. This is reflected by the half-life value of 38 days estimated by Zoeteman et al. (1980).

Heptachlor strongly adsorbs to soils, is relatively persistent and remains primarily within the top few inches of the soils to which it is applied. Degradation products in soil include 1-hydroxychlordene, heptachlor epoxide, α- and β-chlordane and nonachlor. Reported removal rates of heptachlor and its degradation product heptachlor epoxide range from 5.25-79.5% mean loss from soil/year (Sanborn et al., 1977). If the compound strongly adsorbs to soils, significant portions will not be available for hydrolysis, which may account for its longer half-life in soils compared with surface waters.

TABLE 1-1

Selected Physical and Chemical Properties and
Environmental Fate of Heptachlor

Property	Value	Reference
CAS number	76-44-8	
Chemical class:	chlororganic pesticide	
Molecular weight:	373.35	
Vapor pressure:	3×10^{-4} mm Hg (25°C)	U.S. EPA, 1980a
Water solubility:	5.6×10^{-2} mg/ℓ (25-29°C)	U.S. EPA, 1980a
Log octanol/water partition coefficient:	3.87	Hansch and Leo, 1985
or		
Bioconcentration factor:	9500 fathead minnow	Veith et al, 1979
	3800 mosquito fish	Callahan et al., 1979
	3.1×10^4 mosquito larvae	Callahan et al., 1979
	3.7×10^4 snail	Callahan et al., 1979
	2.1×10^4 alga	Callahan et al., 1979
Half-lives in		
Air:	36 minutes (vapor phase) estimated	U.S. EPA, 1986a
Water:	1-3 days	Callahan et al., 1979
	38 days (river)	Zoeteman et al., 1980
Soil:	9-10 months	IARC, 1979
	years	Sanborn et al., 1977

2. ABSORPTION FACTORS IN HUMANS AND ANIMALS

2.1. ORAL

An abstract of a Russian study (Mizyukova and Kurchatiov, 1970) reviewed in U.S. EPA (1980a) reported that heptachlor administered to rats intragastrically in a single oral dose of 120 mg/kg bw was detected in the blood within 0.5-1 hour of administration. Further quantitative data concerning the absorption of heptachlor following oral administration could not be located in the available literature.

2.2. INHALATION

Dorough (1982) exposed rats to ^{14}C-labeled heptachlor vapor at a very low concentration for 1 hour. The total compound inhaled did not exceed 50 µg heptachlor; the rats retained ~87.9%. The protocol followed and measurements made by which the authors estimated percent retention were not specified in this report.

From July 1 to October 4, 1972, Arthur et al. (1975) placed 10 rabbits/sex in open-air cages to expose them to the ambient air of Stoneville, MS, an area of heavy insecticide use. Control rabbits, 10/sex, were housed indoors in an area of low pesticide use. Average air levels of heptachlor epoxide (heptachlor was either not measured or not detected) in open air were 1.86 mg/m^3; levels in the indoor air were not measured. Residues of heptachlor epoxide in adipose tissue were 0.039 ppm in test rabbits as compared with 0.016 ppm in controls. The average respiratory intake of heptachlor epoxide in rabbits from the Stoneville area was calculated at 0.002 µg/day.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1977) conducted an oral subchronic study to determine dose levels of heptachlor to be administered to Osborne-Mendel rats and B6C3F1 mice for carcinogenicity testing. Groups of five male and five female rats and equal numbers of mice were fed diets containing technical grade heptachlor (~73% heptachlor, 22% transchlordane, 5% nonachlor) at concentrations of 0, 20, 40, 80, 160 or 320 ppm (rats) and 0, 20, 40 or 80 ppm (mice) for 6 weeks. After the dosing period, rats and mice were maintained on heptachlor-free diets for 2 weeks. The only parameters examined were food consumption, body weight gain and mortality.

In rats, no effects on body weight gain or food consumption were observed at $\leq$40 ppm in the diet. Female rats fed 80 ppm in the diet had reduced body weight during the first week. Four female rats fed diets containing 160 mg/kg died, while two male and five female rats red at 320 ppm died.

In mice, the highest dose tested (80 ppm) resulted in the deaths of five males and two females. No deaths and no effects on body weight gain or food consumption occurred in mice fed diets containing 20 or 40 ppm.

Shain et al. (1977) fed diets containing heptachlor (99.8% pure) to groups of 42 male Sprague-Dawley rats for 90 days, at an average dose of 0 or 1.29 mg/kg bw/day. In six randomly selected cages, 12 rats showed a statistically significant decrease in mean weekly weight gain ($p<0.01$). This study was designed to determine the effects of pesticides on prostate homeostasis; therefore, histological examinations of other organs were not conducted. Twenty-four hours before sacrifice, rats were castrated.

Cytoplasmic, but not nuclear, androgen receptor site content of the ventral prostate was significantly increased. Ventral prostate protein content was reduced to 13% of levels found in controls and cell number was reduced to 18% of control.

Kinoshita and Kempf (1970) fed rats heptachlor in their diets at various (unspecified) dose levels for 13 weeks. Dose-related increases in the activities of three hepatic microsomal enzymes (phosphorothioate detoxification enzymes, o-demethylase and N-demethylase) were observed. The no-effect level for enzyme induction was reported to be ~1 ppm in the diet.

3.1.2. Inhalation. Pertinent data regarding the subchronic toxicity of heptachlor following inhalation exposure could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Several long-term feeding studies of heptachlor and heptachlor epoxide designed as carcinogenicity studies provide chronic toxicological data. Except for the NCI (1977) and Reuber (1977a,b, 1978) reports, information concerning the other studies was obtained from a review by Epstein (1976).

In an unpublished study by IRDC (1973), groups of 100 male and 100 female CD-1 mice were fed diets containing a 25:75 mixture of heptachlor: heptachlor epoxide at 0, 1, 5 and 10 ppm (mg/kg diet) for 18 months. At 6 months, 10 mice/sex/group were killed. Decreased body weight gain was observed in females fed at the 10 mg/kg diet level. At 6 and 18 months, mean liver weights showed significant dose-related increases in both male and female mice, with the greatest increase in the males. Survival, although underestimated as a result of the interim kill, was 29% for males

and 30% for females at the highest dose and 51-66% for all other groups, including controls. Dose-related increases in liver weights were observed in both male and female mice at termination.

Davis (1965) fed groups of 100 male and 100 female C3H mice diets containing heptachlor at 0 or 10 ppm (10 mg/kg diet) for 2 years. Low survival was observed in both treated (30%) and control (34%) mice. A 2-fold increase over controls in the incidence of hepatic hyperplasia was observed in the test mice. Reevaluation of the slides by four other pathologists resulted in more lesions being classified as hepatomas. In a review of the tissue specimens from the Davis (1965) study, Reuber (1977a, 1978) found hepatic vein thrombosis and cirrhosis in treated but not in control mice; 10% of males and 15% of females had hepatic vein thrombosis and 6% of treated mice had venous occlusion with recent liver infarcts. Thrombosis of the cardiac atrium was also present in some mice with hepatic vein thrombosis. The prevalence of cirrhosis was 5/77 treated females and 2/86 treated males.

Witherup et al. (1955) fed groups of 20 male and 20 female SF rats diets containing 0, 0.5, 2.5, 5.0, 7.0 or 10.0 ppm (mg/kg) heptachlor for 10 weeks. Mortality in the test groups was not dose-related. Body weight loss, decreased food consumption and increased liver weights were observed in treated males, but not in females. These changes were greatest in males fed diets containing 10 ppm. Liver lesions described as "chlorinated hydrocarbon" type and considered to be nonneoplastic were noted in 50% of females and 17% of males fed the 10 ppm diet, and in 17% of females and 38% of males fed the 7 ppm diet. These liver lesions were not observed in rats fed diets containing $\leq$5.0 ppm.

In a study by Jolley et al. (1966), groups of 25 female CD rats received a 75:25 mixture of heptachlor:heptachlor epoxide in their diets at concentrations of 5, 7.5, 10 or 12.5 mg/kg diet for 2 years. A group of 54 control rats were fed insecticide-free diets. Spontaneous lesions were observed in all groups and included multiple cell type hypertrophy, telangiectasia in the anterior pituitary and adrenal hypertrophy. Liver weights were increased over control levels in rats fed at 7.5, 10.0 and 12.5 mg/kg diet.

In the NCI (1977) study, groups of 50 male and 50 female Osborne-Mendel rats and groups of 50 male and 50 female B6C3F1 mice were fed diets containing technical grade heptachlor (~73% heptachlor, 22% transchlordane, 5% nonachlor) for up to 80 weeks. Controls for the rats consisted of 10 matched and 60 pooled untreated rats/sex (controls from concurrent and recent bioassays of other related compounds). For mice, male controls consisted of 20 matched and 100 pooled, while female controls consisted of 10 matched and 80 pooled controls. Despite a preliminary subchronic dose range-finding study, the doses used in this study had to be adjusted because of developing symptoms of toxicity. Low-dose male rats were fed a TWA dose of 38.9 mg/kg diet, high-dose male rats were fed TWA diets of 77.9 mg/kg. Female low- and high-dose rats received TWA doses of 25.7 and 51.3 diet, respectively. Treated diets were provided for 80 weeks, followed by 30 weeks of observation. Male low- and high-dose mice received TWA doses of 6.1 and 13.8 mg/kg diet and female low- and high-dose mice received TWA doses of 9.0 and 18.0 mg/kg diet. Treated diets were fed for 80 weeks, followed by a control diet for 10 weeks of observation.

Mean body weights of high-dose rats were consistently depressed, especially in males. Growth rates of the low-dose groups were similar to controls. Adverse clinical signs including loss of body weight, rough and discolored hair and palpable masses developed in both treated and untreated groups. After 80 weeks, vaginal bleeding developed in some female rats from both treated groups. A dose-related but not significant increase in mortality was observed in male rats. A linear trend test for mortality was significant ($p=0.04$) in female rats.

No differences in body weight gains were observed in mice. Sores and hair loss were observed in both treated and control mice during the first year. Abdominal distention and hair loss were prevalent in high-dose females. Mortality in male mice was similar to controls. In females, there was a significant positive linear trend for mortality, which was due predominately to the difference in mortality between the treated groups.

3.2.2. Inhalation. Pertinent data regarding the effects of heptachlor following chronic inhalation exposure could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Mestitzova (1967), in a study of the effects of heptachlor on the fertility of rats (strain unspecified), fed heptachlor (98.1% pure) in the diet at an "applied dose" of 6 mg/kg bw. It is not clear whether this was a daily dose or a total dose administered over the duration of the treatment. A marked reduction in the litter size in F_1 generations and in one F_2 generation was observed. Mortality in suckling pups was high; during the first week after birth, a mean percent mortality of exposed pups was 46% as compared with 12% in controls. Cataracts developed in pups as well as in treated adults.

3.3.2. Inhalation. Pertinent data regarding teratogenic or other reproductive effects of heptachlor following inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Cote et al. (1985) fed groups of 50 male and 50 female Sprague-Dawley rats a mixture of 15 chemicals, including heptachlor, in the diet for 91 days. The levels of chemicals fed to the rats were 1, 10, 100 or 1000 times the water quality objectives for persistent substances from the 1978 Great Lakes Water Quality Agreement. Results showed no dose-related toxicological changes. Food consumption was significantly lower for females during week 12, though body weight was not affected. The parameters examined included body weight, organ weights, gross and histopathological examination of organs and hematological and biochemical determinations.

The remaining interaction studies examined the effect of various pretreatments on heptachlor toxicity. Sperling and Ewinike (1969) found that pretreatment of adult male rats with an oral dose of 1.8 g turpentine/kg bw/day for 3 days reduced the oral LD_{50} of heptachlor from 112 to 70 mg/kg bw. Intraperitoneal injections of phenobarbital, a known inducer of microsomal enzymes, decreased the LD_{50} of heptachlor in neonatal Sprague-Dawley rats from 531 mg/kg bw in untreated rats to 133 mg/kg bw in pretreated rats (Harbison, 1975).

Scheufler and Rozman (1984) injected male Sprague-Dawley rats intraperitoneally with trans-stilbeneoxide, a phase II enzyme inducer, at 4 mg/kg/on 4 consecutive days. These rats were then given [^{14}C] heptachlor (2 mg/kg) intravenously. Trans-stillbeneoxide significantly increased ($p<0.05$) the cumulative excretion of heptachlor-derived material in the feces, but had no effect on urinary excretion of heptachlor.

A series of experiments (Webb and Miranda, 1973; Miranda and Webb, 1974; Miranda et al., 1973; Weatherholtz et al., 1969) investigated the effects of quantity and the quality of dietary protein on heptachlor toxicity in weanling rats. Heptachlor, administered intraperitoneally, was more toxic to weanling rats fed 10% protein diets, when the protein was high-quality casein rather than low-quality gluten. This effect was more pronounced in rats fed diets containing 18% protein (Webb and Miranda; 1973). Rats fed the gluten diet had reduced body weight, low microsomal protein content and lower activities of heptachlor epoxidase than rats fed the casein diet. It was suggested that metabolism of heptachlor to heptachlor expoxide was inhibited by low protein diets.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenic potential of heptachlor in humans following oral exposure could not be located in the available literature.

4.1.2. Inhalation. Wang and MacMahon (1979) conducted a retrospective mortality study of 1403 white male workers employed for >3 months in two U.S. plants that produce chlordane and heptachlor. The total number of deaths in the cohort was 113 as compared with 157 expected. The observed incidences of all types of cancer, except lung cancer, were less than expected. Twelve members of the cohort died from lung cancer as compared with 9 expected deaths (SMR=134). This increase in lung cancer was not statistically significant. Only one death from liver cancer was observed. Although a statistically significant increase in cerebrovascular disease was observed (17 observed, 9.3 expected; SMR=183), the authors concluded that cerebrovascular disease was not correlated to length of exposure or latency and occurred only after termination of employment and, therefore, was not associated with exposure to heptachlor.

4.2. BIOASSAYS

4.2.1. Oral. Many of the reports concerning the carcinogenic potential of heptachlor have not been published (Davis, 1965; IRDC, 1973; Witherup et al., 1955; Jolley et al., 1966). Information concerning these studies was obtained from a review by Epstein (1976) that was based on a statement of suspension testimony at the Environmental Protection Agency Hearing on Heptachlor/Chlordane, Washington, DC, August 26, 1975. Epstein (1976) also presented the results of independent statistical reanalyses and histological reevaluations of these studies.

In a study by Witherup et al. (1955), groups of 20 male and 20 female CF rats were fed diets containing 1.5, 3.0, 5.0, 7.0 or 10.0 mg heptachlor/kg diet for 110 weeks. Similar groups of rats served as controls. Benign and malignant tumors were randomly distributed among test and control groups, with greater incidences in females, especially those fed 5.0 and 7.0 mg/kg diet. Tumor types observed included lymphomas, osteogenic sarcomas, carcinomas of the thyroid and subcutaneous fibrosarcomas. In rats fed 7.0 and 10.0 mg/kg heptachlor, liver lesions, described as "chlorinated hydrocarbon" type, were observed at a high incidence. These lesions were not believed to be neoplastic. The first statistical analysis indicated that tumor incidences in treated rats were not statistically different from controls. Reanalysis showed significant differences in the incidences of tumors in the treated female groups for any tumor ($p=0.034$), for malignant tumors in rats fed 7.0 mg/kg diet ($p=0.034$) and for any tumor in rats fed 10.0 mg/kg diet ($p=0.017$) (Epstein, 1976). Details concerning the types of statistical tests used in these analyses were not provided.

Jolley et al. (1966) fed groups of 25 female CD rats a 75:25 mixture of heptachlor:heptachlor epoxide at concentrations of 5.0, 7.5, 10 or 12.5 ppm (mg/kg diet) for 2 years. A group of 54 female rats served as controls. At necropsy, spontaneous tumors (e.g., mammary tumors, fibroadenomas) were observed with random frequency among treated and control groups. Malignant lesions of the liver were not observed.

Davis (1965), in a study for the Food and Drug Administration, fed groups of 100 male and 100 female C3H mice diets containing 0 or 10 ppm (10 mg/kg diet) heptachlor for 2 years. A large number of mice were lost or discarded, sacrificed for transplant purposes or died prematurely, so no statistical analysis of the data was made. A 2-fold increase in benign

liver lesions in treated mice over controls was observed in the specimens available for examination. Malignant liver tumors occurred with less frequency in treated mice as compared with control mice. Using the original data and assuming that all missing control mice had tumors and all missing treated mice did not, a statistical analysis was performed. By this method, the incidence of liver tumors in treated mice was not found to be statistically significant from controls.

In a reevaluation of slides from the Davis (1965) study, Reuber (1977b) found the following liver carcinoma incidences: 22/78 (28%) control males, 2/54 (4%) control females, 64/87 (73%) heptachlor males, 57/78 (73%) heptachlor females. Statistical analysis of Reuber's results show a highly significant increased incidence of liver carcinoma in all treated groups when compared with controls ($p=5x10^{-8}$ males, $p=1x10^{-8}$ females). Reexamination of slides from 20 mice by three independent pathologists resulted in concurrence with Reuber's diagnoses; all diagnosed a high incidence of hepatic carcinoma (Epstein, 1976; Reuber, 1977b).

IRDC (1973) fed groups of 100 male and 100 female CD-1 mice a 25:75 mixture of heptachlor:heptachlor epoxide in the diet at 0, 1, 5 or 10 ppm (mg/kg diet) for 18 months. In the original analysis, the incidence of nodular hyperplasia was highly significant for the 5 and 10 mg/kg level males and females when compared with controls. The incidence of hepatomas was lower in the high-dose groups than in the 1 mg/kg diet group and controls. A reexamination of the slides from this study (Reuber, 1977b) found a greater incidence of hepatic carcinoma, with a corresponding decrease in the incidence of hyperplasia and hyperplastic nodules (Epstein, 1976). The incidences of liver carcinoma found by Reuber (1977b) are shown in Table 4-1. Five other pathologi ts reexamined the slides from the IRDC

TABLE 4-1

Carcinogenic Potency of a 75:25 Mixture of Heptachlor Epoxide:Heptachlor Administered in the Diet of CD-1 Mice for 18 Months[a]

Sex	Dose (mg/kg)	Target Organ	Tumor Type	Tumor Incidence (p value)[b,c]
M	0	liver	carcinoma	0/62
	1	liver	carcinoma	2/68
	5	liver	carcinoma	18/68 ($p=2\times10^{-6}$)
	10	liver	carcinoma	52/80 ($p=<1\times10^{-9}$)
F	0	liver	carcinoma	6/76
	1	liver	carcinoma	1/70
	5	liver	carcinoma	6/65
	10	liver	carcinoma	30/57 ($p=5\times10^{-9}$)

[a]Based on Reuber's (1977b) reevaluation of IRDC (1973) slides as reported by Epstein (1976)

[b]Incidence = $\frac{\text{No. tumor-bearing mice}}{\text{No. mice examined}}$

[c]Type of test used not provided

(1973) study and agreed that the incidence of hepatic carcinoma was underdiagnosed in the original examination (Epstein, 1976).

Epstein (1976) also reviewed an Italian study (Cabral et al., 1972) for which an English abstract is available. In this study, a group of 95 Wistar rats, 10 days old, were given heptachlor (96.8% pure) in corn oil by gavage at 10 mg heptachlor/kg bw on alternate days for a total of five doses. Before weaning, 7 rats died, leaving 38 males and 49 females. Twenty female rats and nine males were sacrificed at 60 weeks, leaving 29 females and 30 males to be sacrificed between 106 and 110 weeks. Control rats, 19 males and 27 females, received corn oil alone. The only statistically increased tumor incidence was for endocrine tumors in the male test group (14/19 control vs. 27/30 treated; p=0.033) (Epstein, 1976). In addition, though not statistically significant, rare "lipomatous" renal tumors were diagnosed in two treated females.

In the NCI (1977) study, technical grade heptachlor (~73% heptachlor, 22% trans-chlordane and 5% monochlor) was fed to groups of 50 Osborne-Mendel rats and 50 B6C3F1 mice/sex for 80 weeks, followed by observation periods. The dosing schedules were presented in Section 3.2.1. TWA high- and low-dose diet concentrations were 77.9 and 38.9 ppm (mg/kg diet), respectively, for male rats; 51.3 and 25.7 ppm, respectively, for female rats; 13.8 and 6.1 ppm, respectively, for male mice; and 18.0 and 9.0 ppm, respectively, for female mice. Ten rats/sex served as matched controls and 60 rats/sex served as pooled controls. For mice, 20 male and 10 female matched controls and 100 male and 80 female pooled controls were used. Comprehensive histological examinations were performed on major organs and gross lesions of all rats and mice that died spontaneously, were killed when moribund or were killed at the end of the study, except when precluded because of cannibalism or autolysis.

The results in rats showed no statistically increased (Fisher exact test, life-table method) tumor incidences. No hepatocellular carcinomas were observed in any of the rats. Cholangiocarcinoma was diagnosed in the liver of one low-dose male. Neoplastic nodules of the liver, considered by the investigators to represent a cancerous condition (NCI, 1977) were found in all treated and control groups. The incidences were 2/58 (3%) pooled controls, 1/10 (10%) matched controls, 3/44 (7%) low-dose, 6/49 (12%) high-dose for males and 5/59 (8%) pooled controls, 1/10 (10%) matched controls, 9/48 (18%) low-dose and 5/46 (11%) high-dose for females. Other tumors observed in the rats were follicular-cell and C-cell carcinoma of the thyroid in male and females, mammary tumors in females and two endometrial stromal sarcomas in the high-dose female group.

In heptachlor-treated B6C3F1 mice, hepatocellular carcinoma was the most frequently observed neoplasm. The incidence in high-dose males was significantly different when compared with matched controls ($p=0.001$ or $p=0.0007$ by two simple proportion analyses; $p=0.002$ by life-table method). In low-dose males, the incidence of hepatocellular carcinoma was lower than in the control group. In female mice, high-dose females showed a significant ($p<0.005$) increase in hepatocellular carcinoma as compared with controls. A highly significant ($p<0.0001$) dose-related increase between the low- and high-dose female groups was also observed. This dose-related increase is mainly a result of the large difference between the high- and low-dose groups. The incidence of hepatocellular carcinoma in mice is shown in Table 4-2.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic potential of heptachlor in laboratory animals following inhalation exposure could not be located in the available literature.

TABLE 4-2

Carcinogenic Potency of Heptachlor (78% pure) Administered in the Diet of B6C3F1 Mice[a]

Sex	Dose[b] (mg/kg diet)	Duration of Treatment (weeks)	Duration of Study (weeks)	Target	Tumor Type	Tumor Incidence[c] (p value)
M	0 pooled		90	liver	hepatocellular	17/92
	0 matched	80	90	liver	carcinoma	5/19
	6.1	80	90		carcinoma	11/46
	13.8	80	90		carcinoma	34/47 (p=0.001 or p=0.0007)
F	0 pooled	80	90	liver	hepatocellular	3/78
	0 matched	80	90	liver	carcinoma	2/10
	9.0	80	90	liver		3/47
	18.0	80	90	liver		30/42 (p<0.005)

[a]Source: NCI, 1977

[b]TWA concentration in diet

[c]Incidence = $\frac{\text{No. tumor-bearing mice}}{\text{No. mice examined}}$

(p values calculated using simple proportion analysis)

4.3. OTHER RELEVANT DATA

Heptachlor has tested negative in the reverse mutation assay in 10 strains of Salmonella typhimurium and in three strains of Escherichia coli without metabolic activation (Moriya et al., 1983; Probst et al., 1981; Marshall et al., 1976) and in the rec assay in two strains of Bacillus subtilis in which no activating system was used (Shirasu et al., 1976). Gentile et al. (1982) reported positive results for reverse mutation in S. typhimurium strains TA98 and TA100 at 10 µg technical grade heptachlor/plate with S-9 metabolic activation. A commercial formulation of heptachlor was negative in these strains. Both technical and commercial grade heptachlor were negative for mitotic gene reversion in Saccharomyces cerevisiae with and without S-9 metabolic activation (Gentile et al., 1982). Heptachlor was also negative in the recessive lethal assay in Drosophila melanogaster (Benes and Sram, 1969) and for unscheduled DNA synthesis in rat, mouse and hamster primary hepatocytes (Probst et al., 1981; Maslansky and Williams, 1981).

The dominant lethal assay in CD-1 mice receiving heptachlor by gavage or intraperitoneal injection was negative (Arnold et al., 1977). The dominant lethal assay in rats fed heptachlor at 1 or 5 mg/kg diet for 3 generations resulted in increased numbers of resorbed fetuses (Cerey et al., 1973). An increased number of chromosome aberrations in the bone marrow of these rats was also noted. Heptachlor was positive ($p<0.05$) for unscheduled DNA synthesis in SV-40 transformed human fibroblasts (VA-4) with, but not without, the S-9 fraction at 100 and 1000 µM heptachlor (Ahmed et al., 1977).

4.4. WEIGHT OF EVIDENCE

Heptachlor has been shown to be carcinogenic in mice (NCI, 1977; Davis, 1965; Reuber, 1977b; IRDC, 1973; Epstein, 1976) and rats (Witherup et al., 1955; Epstein, 1976). This evidence of carcinogenicity is sufficient to classify it in weight-of-evidence Group B2, probable human carcinogen, according to the U.S. EPA classification scheme for carcinogenicity (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1978) cancelled the registrations of most pesticide products containing heptachlor (and chlordane) as defined in the notice of Intent to Cancel (U.S. EPA, 1974). The exceptions are "the use of heptachlor or chlordane through subsurface ground insertion for termite control and the dipping of roots or tops of nonfood plants."

U.S. EPA (1975a) proposed 0.0001 mg/ℓ of heptachlor and heptachlor epoxide as the interim primary drinking water standard. This level was deleted in the final U.S. EPA (1975b) regulations because the EPA was involved in the suspension and cancellation proceedings.

FWPCA (1968) set a permissible surface water criteria for public water supplies at 0.018 mg/ℓ for heptachlor and heptachlor epoxide. The criteria for fish and other aquatic life based on an LC_{50} of 0.0002 mg/ℓ for heptachlor would be very low; therefore, it is recommended (FWPCA, 1968) that heptachlor should not be used near an aquatic environment.

U.S. EPA (1980a) determined 2.8 ng/ℓ for heptachlor as the water concentration corresponding to an increased lifetime excess cancer risk of 10^{-5}. This value was derived assuming a 70 kg human consumes 2 ℓ of water/day and 6.5 g of fish and shellfish with a bioconcentration potential of 11,200. Using these assumptions, 97% of heptachlor exposure results from the consumption of aquatic organisms. The value of 2.8 ng/ℓ is based on a q_1^* of 3.37 $(mg/kg/day)^{-1}$ calculated from the incidence of heptocellular carcinoma in male B6C3F1 mice found in the NCI (1977) study with technical heptachlor.

HAs based on noncarcinogenic effects of heptachlor have been determined by U.S. EPA (1987). The 1-day HA is 0.010 and 0.035 mg/ℓ for a child and an adult, respectively. These values, also recommended as 10-day HAs, were derived from a 14-day feeding study in rats by Enan et al. (1982). The lifetime AADI for an adult was determined to be 0.0175 mg/ℓ for a 70 kg adult assuming 2 ℓ water consumption/day, or 0.0035 mg/ℓ, assuming that only 20% of the heptachlor intake is from water. This lifetime value is based on an ADI (now referred to as RfD) of 0.035 mg/day for a 70 kg human derived from a NOEL of 3 ppm (0.15 mg/kg bw/day) in a rat study by Witherup et al. (1955). FAO/WHO (1972) has recommended an ADI of 0.5 µg/kg bw for heptachlor.

ACGIH (1986) adopted a TWA-TLV of 0.5 mg/m³ for heptachlor in workroom air. The OSHA (1985) PEL for skin exposure in the workroom is also 0.5 mg/m³ for heptachlor. NRC (1982) has recommended an interim guideline for airborne heptachlor in military housing of 2 µg/m³.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_s)

Because heptachlor has been shown to be carcinogenic, no RfD_{SI} or RfD_{SO} values for heptachlor will be derived.

6.2. REFERENCE DOSE (RfD)

Because heptachlor has been shown to be carcinogenic, no RfD_I or RfD_O values for heptachlor will be derived.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Four data sets showed significant increases in the incidence of hepatocellular carcinomas in treated groups compared with controls. Tables 6-1 through 6-4 present the tumor incidence for these data sets. A q_1^* of 4.5 $(mg/kg/day)^{-1}$ has been calculated from the geometric mean of these four data sets which showed an increase in hepatocellular carcinoma in mice (U.S. EPA, 1986c). This value will be recommended as the q_1^* for the purpose of this document and the data used to derive it are presented in Tables 6-1 through 6-4. Data were not located within CBI files that would modify this approach to risk assessment.

6.3.2. Inhalation. Pertinent data concerning the carcinogenic potential of heptachlor following inhalation exposure could not be located in the available literature; therefore, an inhalation q_1^* cannot be calculated.

TABLE 6-1

Cancer Data Sheet for Derivation of Potency of Heptachlor in Male C3H Mice

Compound: heptachlor

Reference: Davis, 1965

Species/strain/sex: mouse, C3H, male

Route/vehicle: oral, diet

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Body weight = 0.030 kg (assumed)

Tumor site and type: liver, carcinoma

Human Potency (q_1^*) = 12.4 per mg/kg/day

Experimental Animal Dose (ppm)	Average Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Tumor Incidence No. Responding/ No. Examined
0	0.00	0.000	22/78
10	1.43	0.108	64/87

TABLE 6-2

Cancer Data Sheet for Derivation of Potency of Heptachlor in Female C3H Mice

Compound: heptachlor

Reference: Davis, 1965

Species/strain/sex: mouse, C3H, female

Route/vehicle: oral, diet

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Body weight = 0.030 kg (assumed)

Tumor site and type: liver, carcinoma

Human Potency (q_1^*) = 14.9 per mg/kg/day

Experimental Animal Dose (ppm)	Average Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Tumor Incidence No. Responding/ No. Examined
0	0.00	0.000	2/54
10	1.43	0.108	57/78

TABLE 6-3

Cancer Data Sheet for Derivation of Potency of Heptachlor in Male B6C3F1 Mice

Compound: Technical grade heptachlor

Reference: NCI, 1977b

Species/strain/sex: mouse, B6C3F1, male

Route/vehicle: oral, diet

Length of exposure (le) = 80 weeks

Length of experiment (Le) = 90 weeks

Body weight = 0.030 kg (assumed)

Tumor site and type: liver, carcinoma

Human Potency (q_1^*) = 2.79 per mg/kg/day

Experimental Animal Dose (ppm)	Average Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Tumor Incidence No. Responding/ No. Examined
0	0	0	5/19
6.1	0.79	0.063	11/46
13.8	1.79	0.14	34/47

TABLE 6-4

Cancer Data Sheet for Derivation of Potency of Heptachlor
in Female B6C3F1 Mice

Compound: Technical grade heptachlor

Reference: NCI, 1977b

Species/strain/sex: mouse, B6C3F1, female

Route/vehicle: oral, diet

Length of exposure (le) = 80 weeks

Length of experiment (Le) = 90 weeks

Body weight = 0.030 kg (assumed)

Tumor site and type: liver, carcinoma

Human Potency (q_1^*) = 0.83 per mg/kg/day

Experimental Animal Dose (ppm)	Average Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Tumor Incidence No. Responding/ No. Examined
0	0	0	2/10
9.0	1.17	0.094	3/47
18.0	2.34	0.18	30/42

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APPENDIX

Oral Summary Table for Heptachlor in Male Mice[a,b]

Experimental Dose (mg/kg/day)	Effect	q_1^*
TWA dietary concentration of 0, 6.1, 10, 13.8 or 18 ppm chronic exposure	heptocellular carcinoma	4.5 $(mg/kg/day)^{-1}$ (geometric mean)

[a]Source: U.S. EPA, 1986c

[b]No inhalation data was available; therefore, no inhalation q_1^* could be calculated.